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10/550,608	12/14/2006	Antonio Martinez Martinez	ABG 3008	1313

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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
10/14/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/550,608	MARTINEZ ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-12 and 17-29* is/are pending in the application.

4a) Of the above claim(s) *17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

The preliminary amendment to claims, filed on 07/31/2009, is acknowledged, wherein Applicants have amended claims 1, and canceled claims 2, 3, 5 and 13-16.

Claims 1, 4, 6-12 and 17-29 are pending in this application.

Priority

A claim of priority to application, PCT/EP04/03219, filed on 03/25/2004, is acknowledged. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application SPAIN P200300708, filed on 03/26/2003 without English translation.

Election

Applicant's election with traverse of Group I, Claims 1, 4 and 6-12 in the response filed on 07/27/2009, is acknowledged.

Applicants argue that the Examiner has admitted the existence of a shared technical feature shared by all groups as required by PCT Rule 13.2, and since the Examiner prematurely made at least a partial action on the merits for the sole reason of justifying a restriction requirement, it is respectfully submitted that the restriction requirement is improper.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. According to the PCT Rule 13.2, the technical relationship between the Groups I-V is not a "special technical feature" based on the disclosure of Cappellen et al., and thus, even though a shared technical feature may exist between the groups, it is not a "special technical feature", and unity of invention between the groups does not exist. For the reasons provided herein and in the previous office action, the previous restriction requirement is deemed proper.

Claims 17-29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

The drawings are objected to under 37 CFR 1.83(a) because Figure 1 fails to show details as described in the specification. The contrast setting for Figure 1 is too high (see gel pictures that are completely black). Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any

amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1, 4 and 6-12 are objected to because of the following informalities:

Claims 1, 4 and 6-12 are objected to because the recitation of "FGFR3" should be in parenthesis and follow the phrase it abbreviates when used for the first time in a claim.

Claim 1 (4 and 6-12 dependent therefrom) is objected to because the recitation of the phrase, "and normal references values in samples from subjects without bladder transitional cell carcinoma", can be substantially improved with respect to grammar. The Examiner suggests inserting a verb in the noted phrase. In the interest of

advancing prosecution, the noted phrase is interpreted as "and normal references values are from samples of subjects without bladder transitional cell carcinoma."

Claims 4 and 6-12 are objected to because the recitation of "Method according to…" can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ---The method according to…---.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 4, the phrase "preferably" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being

enabling for an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or to monitor the effect of the therapy administered to the individual with this cancer, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC, does not reasonably provide enablement for an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, *to determine the stage or severity of this cancer in an individual* or to monitor the effect of the therapy administered to the individual with this cancer, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC (italicized for added emphasis). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The breath of the claims. Claims 1, 4 and 6-12 are so broad as to encompass an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, *to determine the stage or severity of this cancer in an individual* or to monitor the effect of the therapy administered to the individual with this cancer, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC (italicized for added emphasis). The

enablement provided is not commensurate in scope with the claim because the specification lacks any disclosure with regard to how specific quantities of FGFR3 correlate to different grades/stages of tumor. In the instant case, the specification enables for an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, or to monitor the effect of the therapy administered to the individual with this cancer.

The amount of direction or guidance presented and the existence of working examples. The specification discloses an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, or to monitor the effect of the therapy administered to the individual with this cancer. However, the specification fails to provide any correlation regarding specific quantities of FGFR3 that can be used to determine the stage, i.e. grade, or severity of bladder TCC in an individual. Without such correlation, one of skill in the art would not know how to "use" the instant methods as claimed because it is unclear how much of the FGFR3 protein have to be differentially expressed to be classified as stage/grade 1 or 2. It is noted by the Examiner that the instant specification is limited to an in vitro method of "detecting" the FGFR3 protein.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. While the art discloses several methods of detecting and quantifying FGFR3 proteins, neither the specification nor the art provide a correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual. In support of this notion, the

Examiner presents a post-filing evidentiary reference of Matsumoto et al. (Fibroblast growth factor receptor 3 protein expression in urothelial carcinoma of the urinary bladder, exhibiting no association with low-grade and/or non-invasive lesions, Oncol Rep. 2004 Nov;12(5):967-71, Retrieved from the Internet <URL:http://www.ncbi.nlm.nih.gov/pubmed/15492779?ordinalpos=85&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum> on 10/05/2009), which states that "no statistically significant relationship was found between FGFR3 expression and tumor grade, invasion" (see Abstract, lines 12-13). Without such correlation, one of skill in the art would not know how to "use" the instant methods as claimed because it is unclear how much of the FGFR3 protein have to be differentially expressed to be classified as stage/grade 1 or 2.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of detecting and quantifying FGFR3 proteins were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process to determine specific ranges of the FGFR3 protein that is differentially expressed in thousands of bladder TCC patients to build a correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual. In the absence of such correlations, one of skill in the art would have to test an essentially infinite number of patients with different stages of bladder TCC progression, and to determine which specific ranges of FGFR3 protein expression correlate with each stage of the bladder TCC.

Therefore, taking into consideration the broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about said correlation between specific quantities of FGFR3 and different stages, i.e. grade, or severity of bladder TCC in an individual, and the high degree of unpredictability associated with making such correlation, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4 and 6-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sturla et al. (FGFR3IIIS: a novel soluble FGFR3 spliced variant that modulates growth is frequently expressed in tumour cells, British Journal of Cancer (2003) 89, pages 1276 – 1284, published online on 09/30/2003) in view of KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007).

Claims 1, 4 and 6-12 are drawn to an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC. See above rejections under 112 2nd paragraph for the claim interpretation.

It is noted by the Examiner that the specification does not define the term "FGFR3", and therefore, it has been interpreted to include any naturally occurring FGFR3 mutants and splice variants.

Sturla et al. teach that FGFR3IIIS protein, a naturally occurring splice variant of FGFR3, is expressed at "very high levels" in bladder TCC cell-line RT112 (see page 1280, right column, lines 2-4, and Figure 3, lane h which corresponds to RT112) using RT-PCR and Southern blotting. Sturla et al. further teach an *in vitro* method to detect the presence of FGFR3 protein in tumor cell-line TC-32 via Immunoprecipitation and Western blotting (see Figures 4 and 5 on page 1281), and b) the comparison of the amount of FGFR3IIIS protein, with reference samples, i.e., cells treated with FGFR3IIIS anti-sense (see Figure 6 on page 1282). Sturla et al. also teach that said FGFR3IIIS

anti-sense treatment is associated with significant growth arrest (see Figure 6 on page 1282).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice an in vitro method to detect the presence of bladder transitional cell carcinoma (TCC) in an individual comprising: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue using Western blotting and immunoprecipitation, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC. A skilled artisan would have been motivated to practice such methods because Sturla et al. teach that FGFR3IIIS is expressed at "very high levels" in bladder TCC cells, i.e., RT112, compared to the normal tissues, making it an excellent marker for detecting the presence of bladder TCC in an individual. Also, it would have been obvious for one of skill in the art to compare the level of the FGFRIIIS of a subject to that of a normal patient. A skilled artisan would have had a high expectation of success because protein detection techniques such as Western blotting and immunoprecipitation, were rampantly used in the equivalent fields as evidenced by Sturla et al. While the reference might not teach a specific embodiment of the claims, i.e., a direct comparison of FGFR3 protein levels in bladder cancer tissues versus normal tissues, the reference Sturla et al. does disclose that there is a significant difference in the expression level of FGFR3IIIS in bladder TCC versus normal tissues via RT-PCR and Southern blotting, and it would have been obvious to

compare the differential expression of FGFR3 protein in patients with bladder TCC from those without the bladder TCC. As discussed in KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), it is considered obvious to combine prior art elements known to be used in equivalent fields of endeavor together into a single combination. The reference clearly shows that the claimed methods were known to be used in equivalent fields of endeavor; thus, it is considered obvious to combine them together. Therefore, the claimed invention as a whole is *prima facie* obvious over the teachings of the prior art.

Conclusion

Claims 1, 4 and 6-12 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

/Nashaat T. Nashed/
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